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| EXAMINER |
|---|
| LUKTON, DAVID |

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/492,392 | Commercon |
| **Examiner** | **Art Unit** |
| David Lukton | 1653 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Sep 28, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *17-33* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *17-33* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Pursuant to the directives of paper No. 12 (filed 9/28/01), claims 17-19 have been amended. Claims 17-33 remain pending. The previously imposed restriction is withdrawn herewith. Claims 17-33 are examined in this Office action.

Applicants' arguments field 9/28/01 have been considered and found not persuasive.

*

An abstract has been submitted. However, the (one) sentence of the abstract is grammatically incorrect. One way of rectifying this deficiency would be to state the following:

Group A streptogramin derivatives of formula I <u>are disclosed</u>...

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In responding to this ground of rejection, applicants have asserted that there exists an example within the "training materials" (1996) in which a hypothetical specification asserted

that a claimed genus of peptides could either be used as an additive in animal feed, or for treating obesity, and, according to applicants, the writer of the training materials concluded that an assertion that an organic compound is useful as an additive for animal feed provides enablement for any and all organic compounds (pharmaceutical compositions being a separate issue). First, no copy of the training materials is available. Second, whatever may be in those training materials is for internal (PTO) use only, and does not necessarily represent a statement of what examiners are required to do or what examiners are prohibited from doing, i.e., the training materials, however accurate the information, does not constitute "ammunition" for patent attorneys to use against examiners. Third, it is the view of the examiner that such an assertion (additive for animal feed) would not pass muster under currently utility (35 USC §101) guidelines, since a utility must be both "substantial" and "credible". Fourth, even if it is true that an assertion of a compound being an additive for animal feed gives an applicant "immunity" from both a utility and an enablement rejection, it does not appear that there is any mention of such in the instant specification (applicants may recite a page and line number, if it is present). Thus, for all of these reasons, applicants' example is irrelevant, or at least not controlling, with respect to the case at hand. Moving on to the question of "pharmaceutical compositions", applicants have argued that if an applicant discloses other compounds, structurally distinct from those being claimed, that is enough to enable "pharmaceutical compositions", since the mere suggestion that the claimed compounds might exhibit the same properties as the prior art compounds is

sufficient to imbue the claimed compounds with the pharmacological attributes exhibited by the prior art compounds. Applicants have also argued that, if an applicant has no idea whether or not a given compound exhibits a particular activity in a given biological assay, the compound in question acquires the property of exhibiting that activity in the biological assay merely by virtue of an applicant suggesting that the compound in question can be formulated into a pill or tablet and adminstered to a human subject. This is obviously untrue. If e.g., arsenic were formulated into a pill, would that cure Alzheimer's Disease?

Applicants have next cited the "Wands factors" and have argued that "all of the methods needed to practice the invention were well known". However, applicants are presumably arguing that the claimed compounds (claim 17) are patentably distinct from any that have been discovered previously. Accordingly, how can applicants argue that it was well known prior to filing that the compounds (of claim 17) were effective to inhibit growth of bacteria? As applicants counsel is aware, the "Wands factors" for evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims [*Ex parte Forman* (230 USPQ 546, 1986)]. Contrary to what applicants have asserted, the specification is entirely devoid of guidance, and of working examples showing antibacterial activity. The key factor here is "unpredictability". As it happens, structure/activity relationships of antibacterial

compounds are unpredictable. Consider, for example, the following:

- Gavini ("Pyridazine N-oxides. III. Synthesis and in vitro antimicrobial properties of N-oxide derivatives based on tricyclic indeno[2,1- c]pyridazine and benzo[f]cinnoline systems", *Archiv der Pharmazie* **333** (10) 341-6, 2000) discloses the preparation and testing of a series of pyridazine N-oxides. With the exception of compounds 3a, 3b, 4b and 5b, the compounds "demonstrated no activity against bacteria" (page 342, col 2).

- Fudou ("Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium. 1. Fermentation and biological characteristics", *Journal of Antibiotics* **54** (2) 149-52, 2001) discloses the isolation of haliangicin which is produced by a marine bacteria; the compound contains a conjugated tatraene moiety and exhibited no antibacterial activity.

- Juvvadi ("Structure-activity studies of normal and retro pig cecropin-melittin hybrids", *Journal of Peptide Research* **53** (3) 244-51, 1999) discloses the preparation and antibacterial activity of cecropin-melittin hybrid peptides. Also disclosed is that the "retro" analogs (the polarity of the amide bond reversed) lost antibacterial activity.

- Avrahami (*Biochemistry* **40** (42) 12591-603, 2001) studied the effects of amino acid substitutions on the antimicrobial activity of amphipathic antimicrobial peptides. Many of the compounds prepared lost antibacterial activity as a result of a single amino acid substitution. Although after-the-fact rationalizations were provided, the observed structure/ activity relationships could not have been predicted *a priori*.

These and other references disclose that there do exist compounds which exhibit no antibacterial activity, and many of these inactive compounds are structurally analogous to compounds that <u>are</u> active. The key point is that the factors which give rise to activity or inactivity are unknown in the art; and certainly applicants have made no attempt to discuss such factors.

With regard to the "pharmaceutical composition", this term carries with it the implied

assertion of therapeutic efficacy. Even if applicants were to provide *in vitro* data, extrapolation to treatment of ill patients would not be enabled. Diseases caused by bacteria include the following:

> Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis, Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, Yellow Fever

Which of these, exactly, do applicants believe that they can treat? If the patient is afflicted with AIDS, are the claimed compounds effective? In addition, there is the problem of antibiotic resistance. Presumably applicants are aware of this, but if not, the following two articles discuss this matter:

> Liu (*Advances in Experimental Medicine and Biology* **455**, 387 1999)
>
> Monroe (*Current Opinion in Microbiology* **3**(5) 496-501, 2000).

Accordingly, (a) one cannot predict antibacterial activity merely by viewing a structure, (b) "undue experimentation" would be required to determine which of the claimed compounds will inhibit bacterial growth, and (c) even if it were true that the compounds exhibited antibacterial activity *in vitro*, "undue experimentation" would be required to determine which of the claimed compounds can be used to treat even <u>one</u> disease caused by bacteria, to say

nothing of the considerable number of diseases that one would have to test for therapeutic efficacy against.

It is suggested that applicants provide at least *in vitro* data that establishes the bacterial growth inhibitory efficacy that has been asserted; also suggested is that the term "pharmaceutical" be deleted from whichever claims recite it.

*

Claims 17-33 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 17 recites (line 3) "any of the foregoing". It should be made clear what is intended here. The best option would be to create a claim that is drawn solely to mixtures.

- To paraphrase what is recited in the first three lines of claim 17, the following is conveyed:

  *A group A streptogramin derivative chosen from:*
  *(a) a compound of formula I*
  *(b) a salts of a compound of formula I*
  *(c) a mixture of stereoisomers of a compound of formula I*
  *(d) a mixture of stereoisomers of a salt of a compound of formula I*

  What the claim conveys is that a streptogramin derivative can be a mixture of stereoismers. However, this runs contrary to the meaning that is recognized in the art for the term "derivative". One can have a mixture of derivatives, but a compound is not converted into a derivative merely because one has a mixture.

- Claim 17 recites the following (beginning at the 8th line from last):

"said mixtures comprise stereoisomers, wherein the carbon bearing $R_1$ is of the R configuration or the S configuration and where said R configuration is predominant"

However, this phrase contains a contradiction. The claim permits the carbon bearing $R_1$ to be of the "S" configuration, but at the same time mandates that mixtures must not only contain some of the "R" configuration (as well as the "S"), but in addition, the "R" configuration must dominate. If the carbon bearing $R_1$ is of the "S" configuration, how can the "R" configuration dominate? A similar issue afflicts the last two lines of claim 17 (for the case of R" being OR'' or $N(R_3)R_4$). The best way to improve clarity would be to create at least one (and preferably) two claims that are drawn to *a mixture of stereoisomers*

- Each of claims 20-24 recite the term "deoxopristinamycin IIA". This term may be used, but only if accompanied by a chemical name or structure.

- Claim 25 makes reference (last line) to the "R" epimer. To which chiral carbon is this referring?
- Claim 25 is indefinite as to the objective and conditions of step (a). The claim encompasses process in which the time and conditions are not effective to form a compound of formula I; it is suggested that the claim be amended to recite that time and conditions are indeed effective in this regard. Claim 25 is also indefinite because it does not require isolation of the final product. If the final product is never isolated, how can it be used? The following format is suggested for process (a) of claim 25:

*A process for preparing... comprising ...*

*(i) reacting a pristinamycin of formula II with an amine of formula III in the presence of a reducing agent for a time and under conditions to form a compound of formula I;*

*(ii) optionally, treating the compound of formula I with an organic or inorganic acid to form a salt of the compound of formula I; and*

*(iii) recovering the compound of formula I or a salt thereof.*

- Claim 25 is rendered indefinite by the phrase:

"capable of generating formaldehyde"

- Claim 26 is indefinite as to the objective and conditions of step (a). The claim encompasses process in which the time and conditions are not effective to form a compound of formula IV; it is suggested that the claim be amended to recite that time and conditions are indeed effective in this regard. Claim 26 is also indefinite because it does not require isolation of the final product. If the final product is never isolated, how can it be used? The following format is suggested for process (a) of claim 26:

  *A process for preparing... comprising ...*

  *(i) reacting a pristinamycin of formula II with an amine of formula III for a time and under conditions to form a first intermediate compound of formula IV;*

  *(ii) reacting the first intermediate compound of formula IV with a reducing agent for a time and under conditions to form a compound of formula I;*

  *(iii) optionally reacting said compound of formula I with formaldehyde, or with a compound which generates formaldehyde in situ for a a time and under conditions to form a second intermediate compound, and subsequently reacting said second intermediate compound with a reducing agent to form a compound of formula I ...*

  *(iv) optionally, treating the compound of formula I with an organic or inorganic acid to form a salt of the compound of formula I; and*

  *(v) recovering the compound of formula I or a salt thereof.*

- Claim 28 makes reference to a "group B streptogramin derivative". However, further information, such as a chemical name or structural formula, is required. The same applies in the ase of claims 29 and 30.

- Claim 32 characterizes diluents and adjuvants as "agents". However, the term "agent" is normally associated with the biologically active ingredient, rather than the inactive carrier. Accordingly, use of term in this way is misleading.

- Claim 32 recites that the presence of diluents and adjuvants is "optional". Note that a composition requires at least two components. Applicants are requested to provide an example of a composition which contains only one pure streptogramin A derivative, but does not contain either a diluent or an adjuvant. Such an example will provide the basis for further discussion. Alternatively, it is suggested that the claim be amended to make the presence of a diluent or an adjuvant mandatory.

- Claim 33 recites that the presence of diluents and adjuvants is "optional". This claim differs from claim 32 in that claim 33 mandates the presence of at least two different compounds, and so is clearly a composition in all cases. The issue, however, is what is meant by the term "pharmaceutical composition". Suppose that there are two chemists. The first combines a Group A streptogramin derivative with a Group B streptogramin derivative, and no diluent or adjuvant is added. Similarly, the second chemist combines a Group A streptogramin derivative with a Group B streptogramin derivative, and no diluent or adjuvant is added. Can applicants provide a specific example in which the first chemist would be preparing a "pharmaceutical composition", but the second chemist would only be preparing a "non-pharmaceutical composition"....? It is suggested that the term "pharmaceutical" be deleted from claim 33.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton. Phone: (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800